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THE CONCEPT OF COLLAGEN DISEASES*

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The term diffuse collagen disease was originally applied to acute and chronic maladies which are characterized anatomically by generalized alterations of the connective tissue, particularly by abnormalities of its extracellular components. In this sense the term can include rheumatic fever, rheumatoid arthritis, polyarteritis, acute lupus erythematosus, generalized scleroderma, and dermatomyositis. A critical consideration of the term is necessary today in order to ascertain whether its frame of reference is useful for further investigation and for the ultimate pathogenetic definition of that group of diseases to which it was originally applied.

The idea that the characteristic organ and tissue alterations in rheumatic fever and rheumatoid arthritis reflect a systemic involvement of the entire connective tissues of the human body was first proposed by Klinge.¹ While not the first observer, he focused attention upon the conspicuous changes of the intercellular components of the connective tissue, the fibrinoid alteration of the collagenous tissue and the myxomatous swelling of the ground-substance. The occurrence of similar connective tissue changes in rabbits made hypersensitive to foreign proteins (Gerlach,² Klinge¹) led him to the conclusion that the tissue damage in human rheumatic disease was due to hypersensitivity. Consequently, Klinge¹ maintained that the same pathogenetic mechanism applied in other disease entities characterized anatomically by fibrinoid connective tissue damage. He therefore included periarteritis nodosa, dermatomyositis, malignant nephrosclerosis, thrombo-angiitis obliterans, certain nephritides, and cardiovascular sepsis (subacute bacterial endo-

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carditis). The observation of fibrinoid vascular lesions in scleroderma led Masugi and Yä-Shu³ to include this disease among the allergic maladies. It was only logical that acute lupus erythematosus in which frequently, though not universally, striking fibrinoid tissue changes were observed, could be interpreted in the same way. Pollack, Baehr, and I⁴ were fully aware of this possibility. However, we believed that such a sweeping biologic-anatomic synthesis was premature. We were cautioned by the fact that local fibrinoid collagen damage occurred in situations where the mechanism of hypersensitivity could be excluded, as in the base of peptic ulcers (Askanazy⁵) and in the vicinity of pancreatic necrosis. The observation of Wu⁶ that trivial mechanical injury provoked fibrinoid collagen alteration in the skin of the rat also challenged the exclusive significance of hypersensitivity in its production. Moreover, we were impressed by the frequency of widespread vascular necrosis, simulating polyarteritis, in experimental hypertension. The recent observations of Byrom and Dodson⁷ who produced fibrinoid arterial necrosis in normal animals by brief rises in intra-arterial tension seem to emphasize the significance of the mechanical factor. Identical vascular lesions had been produced by Winternitz *et al.*,⁸ Holman,⁹ Duff and associates,¹⁰ and by Koletsky,^{11P} as presented today, under experimental conditions in which hypersensitivity could be definitely excluded as a pathogenetic factor. Waters'^{12P} new observation that repeated adrenal-injections produce vascular necrosis is of particular importance because it indicates that arterial lesions simulating human polyarteritis may depend on primary injury of smooth muscle. This might well be of significance in human pathology. These observations also illustrate that an apparent similarity in the histologic picture does not denote identity of tissue lesions and certainly not unity of process and pathogenesis. Holman's^{13P} investigations reflect the same lesson and I shall return to their further significance at a later phase of my presentation. The previously cited experiences led us to the belief that the connective tissue changes demanded further analysis before the question of pathogenesis could be decided. From the preceding observations of Klinge¹ and his followers and our own findings in acute lupus erythematosus we were, however, convinced that a common denominator existed in the striking alterations of the extracellular portions of the connective tissue. Under the influence of the concepts of Schade¹⁴ and of Standenath¹⁵ and of the pathologic-anatomic tradition (Morgagni), we regarded the connective tissue as an organ which we designated as the common seat of these heterogenous maladies. Because of the conspicuous morbid manifestations of the extracellular components, we suggested the

term collagen diseases in a *pars pro toto* sense. I believe today that even this cautious synthesis was premature because it resulted in an indiscriminate acceptance of a term with a diagnostic and pathogenetic import not originally intended when it was conceived. We did not deny the probable rôle of hypersensitivity but we were interested in a search for all factors which might be responsible for the conspicuous structural alterations and, particularly, in the mechanism of their action. It was obvious that such an inquiry had to take its origin from the existing information regarding the structure and the biology of the normal connective tissue, specifically of its extracellular components.

Soon after the connective tissue cells had been discovered by Schwann,¹⁶ the question arose as to the origin of the intercellular substances. In 1861 Kölliker¹⁷ summarized the state of the problem as it was viewed by the majority of investigators of this period.

"In general and in principle," Kölliker wrote, "I agree with Virchow in conceiving of the fibrillar connective tissue as a mere filling portion and of the cells as the significant part. The fibrillar collagenous substance does not directly develop from cells. But the idea that the cells excrete the ground-substance doubtlessly conforms with the belief and concept of many modern histologists; however, I freely agree with Henle that this point of view is not supported by unequivocal facts, because the ground-substance might deposit itself independently. What is meant by the notion referred to above, is in fact not so much that the intermediary substance originates exclusively from the connective tissue cells, but that its chemically characteristic factor is under the direct influence of the cellular elements. I consider that, as in the secretion of a gland, one part of the material is derived from external import but another part from the activity of the cells. Thus, one might assume that mucus and collagenous substances which do not occur in the blood, are formed under the direct influence of cells. I even consider it possible that these substances are formed within the cells, then escape from them and subsequently consolidate."

I have quoted Kölliker so extensively because he clearly poses the problems which today still await an unequivocal answer: (1) the mode of fiber formation, (2) the nature and site of fabrication of the homogeneous ground-substance.

In the years following Kölliker's summary, prevailing opinion expressed itself in favor of his view that the intercellular substances are formed by the fibroblasts. However, observations directly proving this intracellular formation were never supplied and in fact the existence of such cellular activity was seriously challenged by Baitsell's original

tissue cultural and other studies,^{18,19} and by Nageotte's experiments with wound healing.²⁰ Even long before these investigations, von Ebner²¹ had demonstrated that collagen fibers develop in the chorda sheath of lower fish without the presence of mesenchymal cells.

What is the state of our knowledge today? Baitzell¹⁸ in his classical investigations had concluded that fibrin was transformed into a fibrous tissue which in its morphologic structure, to say the least, is apparently identical with normal connective tissue of the frog. Because the newly formed fibers were not resistant to trypsin, he conceded that the ultimate proof of the transformation of fibrin into collagen was still lacking. In 1949 Porter and Vanamee²² demonstrated that the fibers formed in cultures of chick-embryo skin and foregut, rabbit thymus, and rat pericardium show the characteristic periodicity of collagen fibers^{23,24} under the electron microscope and that they resist trypsin digestion. While these experiments prove the collagenous nature of the fibers in tissue culture, the rôle of the fibroblasts in their formation has not been ultimately decided, although Porter and Vanamee stated that the fiber is apparently not spun off the cells. While Baitzell²⁵ believed that fibrous tissue could be formed from a plasma clot by mere mechanical factors without cellular action, Doljanski and Roulet²⁶ maintained that the "fibril-forming process always is the result of a direct interaction (*Fühlungnahme*) between cell and surrounding plasmatic environment." Hass and McDonald²⁷ also expressed the belief "that fibroblasts perform an indispensable rôle in collagen formation" in tissue culture. They showed that cessation of fiber formation was generally associated with morphologic evidence of early fibroblast degeneration, but that "a depression of the pH of the medium to lower limits which permitted continued growth and viability of fibroblasts was usually correlated with a cessation of collagen deposition." These observations illustrate the reciprocal relation between fibroblast and surrounding medium controlling the mechanism of fiber formation and led to their conclusion that "normal fibroblasts and normal mediums interact to yield collagen *in vitro*."

I have dealt at this length with the *in vitro* formation of collagen fibers because the situation of fibroblasts within culture medium can be likened to the conditions of the connective tissue in the living. Indeed, Doljanski and Roulet²⁶ considered the intercellular substratum as the ground-substance of the culture analogous to the homogeneous ground-substance of the connective tissue *in vivo*. This point of view is of significance because it conforms with the idea of Nageotte,²⁰ who maintained that the fibroblasts in the animal body do not produce the intermediary substance

which is furnished rather by the body fluids. Certainly information gained from experimental variations of the culture medium, such as studies of cell cultures in synthetic media (A. Fischer,²⁸ and Morgan, Morton, and Parker²⁹) and particularly of tissue culture in plasma of patients with various diseases, could advance our knowledge of the connective tissue in normal and morbid states. Investigations of the simpler system of tissue culture are more likely to clarify the problem of normal and abnormal fiber formation than those of the complex conditions of the living animal. Yet, investigations of the living animal may result in observations which do not correlate with those reached with the method of tissue culture. Hass and McDonald²⁷ found that low ascorbic acid values had no influence on collagen production in the isolated system of the tissue culture. Their findings contrast with those of von Jeney and Törö³⁰ who came to the conclusion that collagen fiber formation was promoted by the addition of ascorbic acid to the culture medium.

Wolbach and Howe³¹ are credited correctly with the important discovery that ascorbic acid is essential for the formation of collagen fibers; but the process involved has not yet been fully clarified (Reid³²). Wolbach and Bessey³³ tentatively suggested that the mode of action by which ascorbic acid promotes the formation of collagen "may be involved in the chemical mechanisms (enzymes) of the cells responsible for the synthesis of this protein product." Danielli, Fell, and Kodicek³⁴ believed that ascorbic acid deficiency affects the fibroblasts which show a reduced degree of phosphatase activity. On the other hand, Penney and Balfour³⁵ recently reported that there is a failure in the production of acid mucopolysaccharides in the wounds of a guinea-pig depleted of vitamin C. These observations have been confirmed by our own investigations. On the other hand, Gersh and Catchpole,³⁶ in a more recent publication, stated that there is an increased amount of ground-substance in scorbutic guinea-pigs. They stressed the fact that much of this ground-substance consists of alcohol-insoluble, water-soluble glycoproteins. The latter are, in their opinion, in a state of depolymerization. The differences in the amount of ground-substance in these two sets of experiments may depend on the difference in staining technics used. The results need not be considered as incompatible, inasmuch as both observations reach the conclusion that the ground-substance is abnormal in scurvy. Both tend to show that not only normal fibroblasts but also a homogeneous ground-substance, adequate in amount and in chemical or physicochemical constitution, is of paramount importance for the formation of collagenous fibers. The fact that changes in ground-substance and collagen fibers are so striking in the so-called collagen

diseases makes it evident that a fuller understanding of alterations in the elaboration and constitution of these materials is needed to clarify their pathogenesis.

One is intrigued also by the question as to the mode of action of the adrenal cortex and other hormones upon the formation of collagen fibers. The investigations of Taubenhaus and Amromin³⁷ have shown that desoxycorticosterone stimulates fibroblasts and encourages the deposition of collagen around sterile abscesses, while testosterone and estradiol inhibit fibroblastic response and collagen formation. The investigations of the New York Presbyterian Hospital Group^{38P} and of Spain and associates^{39P} have shown cortisone to have a marked inhibitory effect in experimental wound healing. I should like to refer also to the inhibition of anaphylactic⁴⁰ and anaphylactoid⁴¹ tissue reactions by ACTH. On the other hand, Baggenstoss^{42P} has demonstrated a marked fibrosing effect of cortisone in patients with polyarteritis. In one case of acute lupus erythematosus treated with ACTH, I could still see acute fibrinoid alterations of the connective tissue, while in another case there was increased fiber formation in the heart, but the fibers seemed to be abnormal because of irregularity in width and staining quality. It should be added that in both cases "L.E." cells⁴³ were persistently found during life and hematoxylin bodies⁴⁴ were present in several organs post mortem. These divergent experimental and pathologic-anatomic observations are difficult to interpret. The inhibition of fibroblastic response seems to indicate a direct influence of the adrenal hormones upon the cells. But the experience with tissue cultures shows that fiber formation is the result of interaction between fibroblasts and medium. By analogy, a possible action of the hormones directly upon the formation of the extracellular substances or upon their chemical reactivity and physical state also must be taken in consideration. I shall return shortly to some observations which point in that direction.

The mucinous nature of the homogeneous ground-substance has been known for decades (Rollett⁴⁵). The investigations of Karl Meyer⁴⁶ and his associates have greatly advanced our knowledge of the mucopolysaccharides which enter into its constitution. They are mainly hyaluronic acid and chondroitin sulfuric acid. The occurrence and influence of depolymerizing enzymes (hyaluronidase) and their relation to the spreading factor of Duran-Reynals⁴⁷ has been clarified by Meyer and others. The development of specific inhibitors and the occurrence of a non-specific antihyaluronidase have been demonstrated by Glick.⁴⁸ The rôle of such inhibitors is equal in importance to that of hyaluronidase under normal and abnormal conditions. The opposite effects of luteinizing and follicular hormones upon the spreading of dyes in the rabbit

skin (Sprunt and McDearman⁴⁹) and the inhibition of hyaluronidase by desoxycorticosterone (Seifter *et al.*⁵⁰) demonstrated the influence of hormones upon the interaction between hyaluronic acid and hyaluronidases. The presentation of Rinehart and Greenberg^{51P} shows that pyridoxine deficiency causes a striking deposition of metachromatic substance in the arterial wall.

It is generally accepted that the mucopolysaccharides are linked to proteins within the ground-substance (Ropes *et al.*⁵²). Very little is known about the chemical constitution of the protein moiety and its modifications under normal and abnormal conditions. It is digested by trypsin, as experiments of Day⁵³ have shown. That it contains tyrosine is indicated by the fact that the xanthoprotein reaction of connective tissue is abolished after removal of the ground-substance by baryta water (Rollett⁴⁵). Ogston and Stanier⁵⁴ recently reported that synovial fluid contains hyaluronic acid in close association with protein; the latter constitutes about 30 per cent of the complex. The amino acid partition was studied by paper chromatography.

From this very superficial review of the chemical nature and of certain physiologic factors concerning the ground-substance, it is obvious that microscopic investigations of its structure in normal and abnormal conditions are of paramount importance. This task is restricted by technical difficulties partly inherent in the easy solubility of the mucopolysaccharides in the conventional fixatives. Preparation by freezing and drying is obviously the ideal technic but unfortunately it cannot yet be applied routinely in the investigations of pathologic-anatomic material. However, the examination of the connective tissue in the disorders under consideration has revealed conspicuous alterations of the homogeneous ground-substance. Klinge¹ referred to its myxomatous swelling in rheumatic fever and I⁵⁵ have stressed the same feature in acute lupus erythematosus and have demonstrated an intense toluidine blue metachromasia, which was abolished by preceding treatment of the sections with bull-testis hyaluronidase.

Such morphologic observations urge upon the medical investigator the desire to understand the mechanism by which these structural alterations are provoked in disease. He tries to correlate his observations with the facts known to chemists and physiologists, but he soon realizes that certain fundamental problems regarding the nature and origin of the homogeneous ground-substance are as obscure as in the days of Kölliker.¹⁷ Vaubel⁵⁶ has studied the problem of intracellular mucin formation in tissue cultures of synovial cells and of fibroblasts. He found mucin in the supernatant fluid of cultures of the former, but no mucin in fibroblast culture medium. In Wolbach's⁵⁷ classical experi-

ments the appearance of vacuoles in fibroblasts and the accumulation of a non-fibrillar intercellular substance pointed to the fibroblasts as the manufacturers of this material. But the reinvestigations of the developing granulation tissue in scorbutic guinea-pigs by Penney and Balfour³⁵ revealed fat within these vacuoles and a failure in the production of mucopolysaccharides. We have made similar observations.

Moreover, in experiments by Ludwig and Boas,⁵⁸ designed to study the rôle of hormones in the deposition of ground-substance, newborn chicks have been injected with testosterone. Relatively large amounts of metachromatic substance appeared in the comb within 12 days, while control birds did not show significant amounts of mucopolysaccharides. While the fibroblasts were conspicuously large and showed cytoplasmic basophilia and phosphatase activity, no metachromatic material could be detected within them. The metachromasia of the ground-substance was abolished by preceding treatment of the sections with bull-testis and streptococcal hyaluronidase, and Boas⁵⁹ extracted large amounts of hyaluronic acid from the cock's comb. It should be added that the injection of estrogen, adrenal cortex extract, and of cortisone did not cause deposition of metachromatic ground-substance.⁶⁰

In another series of experiments Ludwig, Boas, and Soffer⁶¹ treated thyroidectomized guinea-pigs with thyrotropic hormone. They all developed exophthalmos. Within the connective tissue of the orbital structures a distinct increase in the amount of metachromatic material was noted. Identical changes were seen in the retroperitoneal tissues. Chemical examination revealed a rise in hexosamine content of these tissues with an increase in water content and an elevation of serum hexosamines. These observations again demonstrated that the deposition of mucopolysaccharides is under hormonal control, a fact well known from experience with myxedema and with pretibial myxedema in hyperthyroidism (Watson and Pearce⁶²), and from experiments of Selye,⁶³ Ogston and associates,⁶⁴ and others. Yet neither our experiments nor those of others brought forward conclusive evidence that the mucopolysaccharides are formed by fibroblasts. On the other hand, Gersh and Catchpole³⁶ in a recent paper showed the presence of granules positive to the periodic-acid, sulfurous-fuchsin technic in fibroblasts in situations where ground-substance is laid down. They interpreted these granules as glycoprotein and expressed the belief that their observations proved a secretion of ground-substance by fibroblasts. Obviously their conclusions rest on chemical identification by the McManus stain. From what we have learned from McManus^{65P} today it seems to me that he would not go that far, and that his only claim regarding chemical identification is that substances stained by his method contain carbohydrates.

In view of the great diversity of tissue components and other substances stainable by the technic, great caution must be exercised in the dynamic interpretation of microscopic pictures. However, the paper by Gersh and Catchpole³⁶ contained other observations which are of great importance. Because these refer to variations in stainability of the same reactive material before and after extraction with water, such differences cannot depend on chemically different substances. Gersh and Catchpole believed that such variations are determined by changes in polymerization of the glycoproteins of the ground-substance. It would be highly desirable to apply the same technic of water extraction to pathologic material in order to analyze the nature of the changes in the ground-substance which are so conspicuous in rheumatic fever and acute lupus erythematosus. It is evident that neither the chemical nature of the ground-substance nor the site of its manufacture is sufficiently clarified.

An abnormality of the ground-substance might be determined by a disturbance of cellular enzymatic activity *in situ*. For instance Janeway⁶⁶ recently has suggested that antibody antigen union in sensitized animals could lead to the release of enzymes from connective tissue cells. But it is also conceivable that abnormality of the ground-substance is correlated with abnormality of the blood plasma, which necessarily provides the chemical building blocks for its formation. This possibility is suggested by our experiments with thyrotropic hormones and by the fact that in acute lupus erythematosus, with its increase in mucinous ground-substance, the hexosamines are always strikingly elevated in the blood serum. It is of significance that they are decreased by treatment with cortisone and ACTH. Further investigations correlating serum hexosamines and the amount and quality of mucopolysaccharides in connective tissue certainly are needed. In reference to the protein moiety of the ground-substance, Coburn and Moore⁶⁷ and Teilum⁶⁸ expressed the belief that glomerular capillary changes in acute lupus erythematosus could be the result of a precipitation of globulins which are so persistently elevated in this disease. The conspicuous changes in the serum proteins in this disease are distinctly influenced by cortisone and ACTH. Miss Reiner, in our laboratories, found that serum-albumin levels rise, while gamma globulins are decreased under cortisone and ACTH treatment. The alpha 2 globulin partition, however, which is also elevated, remains unchanged. Holman's^{18P} investigation seems to point also in the direction that some change, not yet defined, of the blood plasma could be responsible for necrotizing alterations of the vessel wall. Parenthetically, mention should be made of the recent report of abnormal lipoprotein macromolecules in the blood plasma of arteriosclerotics.⁶⁹ Hase-
rick's^{70P} discovery of an abnormal antigenic constituent of the plasma

in acute lupus erythematosus, associated with the gamma globulins, adds further evidence for the importance of blood plasma changes in the pathogenesis of one of the members of the group. The inclusions of the "L.E." cells have recently been shown by Lee and associates⁷¹ in our laboratories to contain depolymerized desoxyribose nucleic acid, similar to the hematoxylin-stained bodies in the tissues of acute lupus erythematosus. Haserick's factor is therefore apparently responsible for this peculiar disturbance of nucleic acid metabolism of mesenchymal cells. Its relation to the changes in the intercellular substance in acute lupus erythematosus is not clear, although the association of nuclear changes with fibrinoid alterations of connective tissue is sometimes striking in vessels and in the heart.

The fibrinoid collagen change has always dominated the discussion of the structural alterations of the group referred to as collagen diseases. In fact, it has been singled out as the basic principle for pathogenetic explanation. I do not want to repeat my reasons for not accepting the thesis that fibrinoid alteration of collagen in human disease is pathognomonic for hypersensitivity. More information is needed regarding the composition of the substance referred to as fibrinoid before we indulge in biologic-anatomic correlations. The term as originally applied by Neumann⁷² referred to collagen fibers which assume the structural and tinctorial quality of fibrin. This alteration of the fibers was believed to be the result either of an impregnation of the intact or degenerated collagen fiber with fibrin or of a disintegration of the collagen fiber without additional fibrin impregnation (Ricker,⁷³ Bahrmann⁷⁴). Klinge¹ spoke of a transformation of the connective tissue substance with the formation of waxy, highly refractive masses and believed that fibrinoid degeneration of connective tissue is the result of swelling and chemical alteration of the ground-substance. Altshuler and Angevine⁷⁵ also believed that the ground-substance is the only constant anatomic element in the formation of fibrinoid and that it is formed by precipitation of the acid mucopolysaccharides. They assumed that the precipitant is probably an alkaline protein derived from tissue necrosis or the interaction of the tissue with a damaging agent. These conclusions are of great interest because they indicate that abnormal fibrils may be formed in the ground-substance instead of the typical collagen fibers. It is not permissible also to assume that a primary abnormality in chemical constitution of the ground-substance due to imperfect formation might be responsible for the appearance of abnormal fibers with the characteristics of fibrinoid? These are merely working hypotheses which should be pursued by further investigations. Again, tissue cultures with well designed variations of the nutrient media might clarify the problem.

But the constitution of the fibrinoid material could also come under direct attack with methods other than those of conventional histopathology. The presentation of Gross^{76P} and his previous work have shown the intrinsic value of the electron microscope for the identification of the ultrastructure of the normal collagen fiber. Application of this fundamental method to the connective tissue in morbid states, as shown by Gale,^{77P} is certainly most desirable. One is aware that such difficult investigations will not mature for a long time and will require further advances of technic, such as microsections. We have used x-ray diffraction in the examination of subcutaneous nodules of rheumatoid arthritis and endocardial vegetations of acute lupus erythematosus. The pattern obtained was that of fibrin, but x-ray diffractionists inform me that the term fibrin-pattern covers substances of a wider range than fibrin only. I believe that the methods described by Hass^{78P} for the analysis of amyloid could well be applied to the investigation of the same material.

When we originally proposed the term collagen diseases we were aware that the structural alterations which had been disclosed by the conventional technics of microscopic anatomy required further analysis. We believed that the visible alteration of the intermediary substances was only a manifestation of a profound disturbance of their chemical and physical constitution. We recognized that the morphologic observations did not constitute a pathogenetic definition of the maladies grouped together and that the term did not imply identifying them with one another. We realized that a rational inquiry into the pathologic states of the collagenous material must be based upon a full comprehension of its normal constitution and biology. We did not fully realize the depth of this problem at that time. I have tried to outline today not only how fragmentary our knowledge still is but also how rapid is the tempo of new advances. The fundamental question of fiber formation will be brought to a solution by tissue culture and electron microscopy. The chemical nature of the homogeneous ground-substance, its origin, and the influence of enzymes and hormones upon its constitution are under vigorous scientific attack. A never-relaxing concentration upon these problems has convinced me that the concept of collagen diseases is not an idle speculation. The increasing interest of the medical profession could support me in my conviction; but the impatience of clinical investigators and a peculiar worship of diagnostic terms have led to an exaggerated popularity of the diagnosis collagen disease. There is danger that it may become a catch-all term for maladies with puzzling clinical and anatomical features. It is not a term applicable to diagnosis and certainly does not define the morbid process of the diseases grouped together. All we wanted to express originally was that in certain diseases

anatomical investigations reveal conspicuous alterations of the intermediary substances of the connective tissue in a systemic manner. Today, in selecting the title "Concept of Collagen Diseases" I took advantage of the definition of the word concept, which means an idea that includes all that is characteristically associated with or suggested by a term. In the present uncertainty of our knowledge regarding the origin of the intermediary substances and of the factors which regulate their structure as well as chemical and physicochemical constitution, it seems obvious that alterations of this material cannot be regarded as maladies of these substances or of the connective tissue as a whole. These morphologic disorders are only outward manifestations of morbid processes, the site and nature of which are still obscure. When further basic research has clarified the factors which control the plasticity of the connective tissues under normal and abnormal conditions, the concept of collagen disease will well have served its purpose.

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